Paediatric sepsis and multiple organ failure

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Mortality from paediatric sepsis and multiple organ failure has fallen over the last half century, but both remain significant causes of death and morbidity among children and infants in the intensive care unit. This article provides a basic guide for front-line clinicians involved in paediatric resuscitation, addressing nomenclature, epidemiology and suggestions for early treatment.

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The interpretation of early studies concerning the epidemiology, pathophysiology and treatment of sepsis was hampered by inconsistencies in terminology. In these studies, 'sepsis' could refer to a variety of phenomena, from positive microbial cultures through to shock. This problem was addressed in 1992 in a consensus document, which offered standardized, clinically-based definitions for both the 'septic spectrum' and organ failure (Bone et al, 1992).

The consensus statement also introduced the concept of the systemic inflammatory response syndrome (SIRS), which, as it's name suggests, represents generalised activation of the innate immune response following a variety of stimuli. Diagnostic criteria for SIRS are outlined in *Figure 1*. It is thought that SIRS represents a precursor to multiple organ failure (MOF). The stimulus for SIRS may be non-infective (such as trauma), or infective, in which case it is classified as sepsis. Sepsis associated with signs of end-organ hypoperfusion (e.g. a rise in blood lactate) is defined as severe sepsis. If severe sepsis is associated with ongoing hypotension after fluid resuscitation, it is called septic shock. Criteria for individual organ failure are shown in *Table 1*, MOF requires two or more simultaneous organ failures. It is important to note that the development from SIRS to MOF is not always linear, in that any of the precursor entities can progress directly to MOF.

Interestingly, the above definitions of the septic spectrum do not mandate positive microbiological cultures, but merely a strong clinical suspicion of an infecting organism. This approach was chosen to reflect clinical practice, because up to 50% of cases of severe sepsis are culture negative (Wilkinson et al, 1987). This approach also provides the clinician with rapid bedside criteria to facilitate entry into clinical trials. A criticism of this has been that it creates diagnostic criteria that are overly sensitive and may paradoxically hinder trial interpretation by increasing patient heterogeneity. An expert group convened to re-examine these definitions,

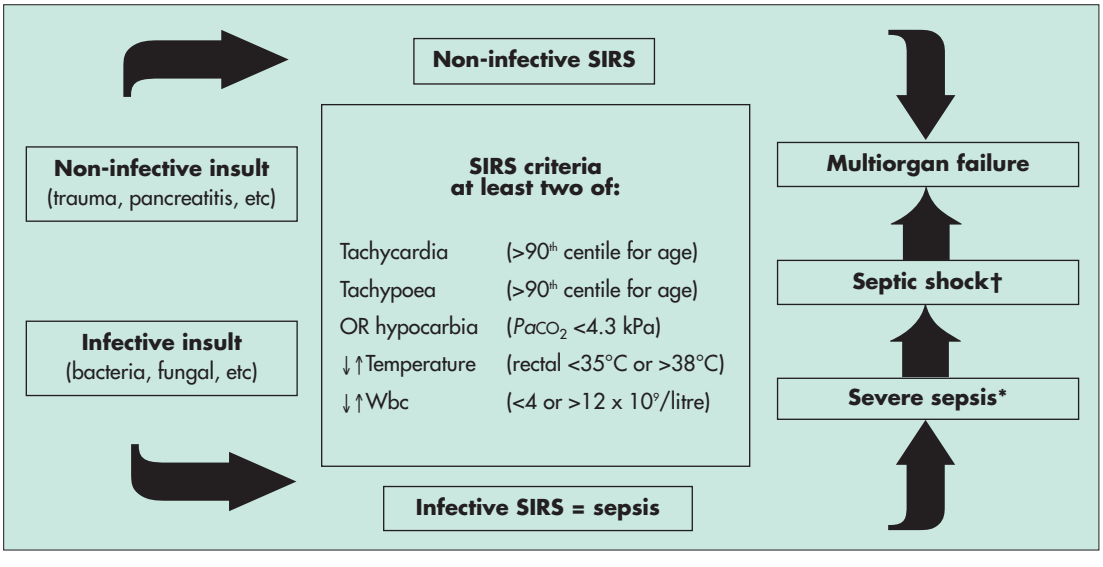


*Figure 1. Relationship between the systemic inflammatory response syndrome (SIRS), septic entities and multiple organ failure. *Severe sepsis requires signs of end-organ hypoperfusion, including raised blood lactate, altered mental status. decreased urine output. †Septic shock refers to hypotension (blood pressure <2 standard deviations for age) following adequate fluid resuscitation. Wbc = white blood cell count.*

both in response to this criticism and to new pathophysiological insights into sepsis (Levy et al, 2003) concluded that the definitions remain robust, but postulated a more sophisticated staging system for the sepsis known as PIRO (Predisposing factors, Infecting organism, Response, Organ dysfunction), somewhat akin to the tumor node metastasis staging for cancer.

EPIDEMIOLOGY

A large study from the US examined 1.6 million hospital discharges during 1995, and documented an incidence for severe sepsis of 0.6 cases per 100 hospital discharges, equating to a population incidence of 0.56 cases per 1000 children (Watson et al, 2003). This was highest in the those aged 0–12 months (5.2 cases per 1000 population), decreasing in older children to rates between 0.20 and 0.50 per 1000. Sex differences were found for infants only, with a slight male preponderance (5.5% vs 4.5%). Interestingly, the mortality was fairly consistent across all ages (9.6–13.5%), but was influenced strongly by both the presence of significant comorbidity and the site of infection. These associations varied with age; infant mortality more than doubled in the presence of renal, haematological, immunological and neoplastic abnormalities, while comparable increases in mortality among younger children (aged 1–9 years) were seen with concurrent cardiovascular, haematological and immunological disorders. The associations for older children (aged 10–19 years) were similar, with the addition of respiratory and renal diseases. With regard to site of infection, endocarditis doubled mortality in all age groups, central nervous system infection was important in the two youngest age groups and bacteraemia in the two oldest age groups.

This study, however, did not document all causative organisms. High mortality rates were seen with *Meningococcus* (20%, 10% and 15% across the three ascending age groups). Contemporary studies from UK paediatric intensive care units (ICU) suggest that the mortality from this organism is now lower, between 6% and 9% (Booy et al, 2001, Thorburn et al, 2001).

Unfortunately, not much is known about temporal trends in sepsis among children. Adult data demonstrate that the epidemiology of sepsis has changed considerably over the two decades between 1979 and 2000 (Martin et al, 2003). The incidence has trebled over this time (from 83 to 240 cases per 100 000 population). Although this has resulted in more deaths from sepsis, the in-hospital mortality has fallen from 28% to 18%, with the greatest improvement occurring among patients having less than three organ failures. The profile of causative organisms has also altered, possibly as a result of an increase in nosocomial infections: gram-positive bacteria overtook gram-negative organisms as the leading cause in 1987, and fungal infections, although less common, have increased by over 200%.

The estimated ICU incidences for components of the septic spectrum are: SIRS 82%, sepsis 23%, severe sepsis 4% and septic shock 2% (Proulx et al, 1996). The cumulative risk for developing each of these entities increases with length of ICU stay. The incidence of MOF varies from 11% to 27% (Wilkinson et al 1986, 1987, Proulx et al, 1994, 1996; Goh et al 1999), although a study from Peru documented a higher rate of 57% (Tantalean et al, 2003).

Paediatric MOF typically occurs within 1–2 days of ICU admission, with the respiratory (68–95%), cardiovascular (36–84%) and neuro-

TABLE 1.
Definitions of organ failure

Organ system	Criteria (occurrence of any one criterion constitutes organ failure)
Cardiovascular	Systolic blood pressure <40 mmHg (infants), <50 mmHg (children)
	Heart rate (beats per minute) <50 or >220 (infants), <40 or >200 (children)
	Cardiac arrest
	Serum pH <7.20 (with a normal *Pa*CO2)
	IV infusions of inotropes to maintain blood pressure and/or cardiac output
Respiratory	Respiratory rate (breaths/minute) >90 (infants), >70 (children)
	PaO_2 <40 Torr (absence of cyanotic heart disease)
	$PaCO_2$ >65 Torr (absence of chronic lung disease)
	PaO_2/FiO_2 <200 Torr (absence of cyanotic heart disease)
	Mechanical ventilation (>24 hours if postoperative)
Neurologic	Glasgow Coma Scale <5
	Fixed, dilated pupils
	Persistent (>20 minutes) intracranial pressure >20 Torr, or requiring therapeutic intervention
Renal	Serum urea >36 mmol/litre
	Serum creatinine >180 mmol/litre (absence of pre-existing renal disease)
	Renal replacement therapy (dialysis or haemofiltration) for renal reasons
Haematological	Haemoglobin <50 g/litre
	White blood cell count <3000 cells/mm^3
	Platelet count <20 000 cells/mm^3
	Disseminated intravascular coagulopathy (PT >20 sec, or APTT >60 sec with presence of fibrin split products)
Hepatic	Total bilirubin >85 mmol/litre and serum ALT or AST > twice normal (without evidence of haemolysis)
	Hepatic encephalopathy > grade 2

ALT = alanine transaminase; APTT = activated partial thromboplastin time; AST = aspartate transaminase; PT = prothrombin time. From Wilkinson et al (1986, 1987).

logical (27–65%) systems being the most commonly affected. The overall mortality for MOF is 36–57%; this increases with either a greater number of organs failing simultaneously or when the onset of MOF is delayed relative to ICU admission ('secondary MOF'). It has been estimated that MOF contributes to between 92% and 100% of all ICU deaths. Interestingly, the proportions of septic and non-septic MOF are similar, with comparable mortality rates. The reasons for progression from SIRS/sepsis to MOF are unknown; however, several excellent reviews on this topic are available (Brun-Buisson 2000; Butt 2001; Despond et al 2001; Hotchkiss et al 2003). The importance of genetic factors is increasingly recognized (Holmes et al, 2003).

EARLY TREATMENT

The principles of early treatment for the septic infant or child are similar to those for adults; appropriate antibiotic coverage, early aggressive fluid resuscitation and timely cardiorespiratory support. Specialized and organ-specific therapies typically occur in the ICU, and will not be covered in this article, but reviews are available (Vincent et al, 2002).

ANTIBIOTIC THERAPY

Choice of antibiotic should be guided by patient age, immunization status, relevant co-morbidity and presumed site of primary infection, as well as knowledge of local resistance patterns. Inappropriate empiric therapy is associated with a near doubling of mortality (from 37% to 69%) in critically-ill adults (Valles et al, 2003), and a four-fold increase in the paediatric death rate (from 4% to 17%, adjusted odds ratio 5.1, Leibovici, 1998). Selection of an inappropriate antibiotic is 2.5 times more likely when the primary site of infection is unknown (Valles et al, 2003). The most common site of origin for severe sepsis in neonates is primary bloodstream infections (42%), and, in children, the respiratory tract (46%) (Watson et al, 2003). Overall, *Staphylococcus*, *Streptococcus* and *Meningococcus* are the three most common community-acquired bacteria. Methicillin-resistant *Staphylococcus* now accounts for 13% of staphylococcal bacteraemia in the UK, increasing thirteen-fold between 1990 and 2000 (Khairulddin et al, 2004).

FLUID RESUSCITATION AND HAEMODYNAMIC SUPPORT

Severe sepsis produces variable degrees of myocardial depression, capillary leak and loss of vascular tone, as well as activation of the coagulation cascade. Compared with adults, children often manifest severe hypovolaemia, and appear more prone to myocardial depression. Detailed guidelines from the American College of Critical Care Medicine on paediatric haemodynamic support are now available (Carcillo et al 2002) (*Figure 2)*; these recommendations have been incorporated into the Paediatric Advanced Life Support manual (Chameides and Hazinski, 2004). The impact of timely, and appropriate, resuscitation by primary-care clinicians was demonstrated in a 9-year, retrospective study (Han et al, 2003). The authors showed that resuscitation consistent with the above guidelines was associated with a disease severity-adjusted, 6.8-fold increase in survival. Conversely, every hour of delay in effective resuscitation produced an increase of 0.5 in the mortality odds ratio. The principles of cardiorespiratory support are discussed briefly below.

Fluid resuscitation

Early, aggressive fluid resuscitation (>40 ml/kg within the first hour) is vital. The survival benefit from this approach was documented over 13 years ago (Carcillo et al, 1991), and is now recommended in the major paediatric life-support manuals. It is not unusual for severe cases to require up to 200 ml/kg in the first 24 hours. Controversy exists as to the choice of resuscitation fluid; many texts recommend crystalloid, although a large study has shown that albumin is a safe alterntive (Finfer et al, 2004). Fresh frozen plasma is useful, primarily to correct clotting abnormalities. However, rapid administration should be avoided because of the potential for vasodilatation secondary to vasoactive kinins. Blood should not be used as an acute volume expander (unless in the setting of trauma with ongoing haemorrhage), but the contribution of haemoglobin to oxygen delivery must be considered. One large study (Rivers et al, 2001) targeted a haemoglobin concentration of 10 g/dl as part of the resuscitation protocol when signs of inadequate oxygen delivery were present (central venous oxygen saturation less than 70%); others have endorsed this approach (Carcillo et al 2002). Most authors would agree that there is no place for hypotonic fluid administration (for both resuscitation and maintenance fluids) in the setting of severe sepsis or MOF (Duke and Molyneux, 2003).

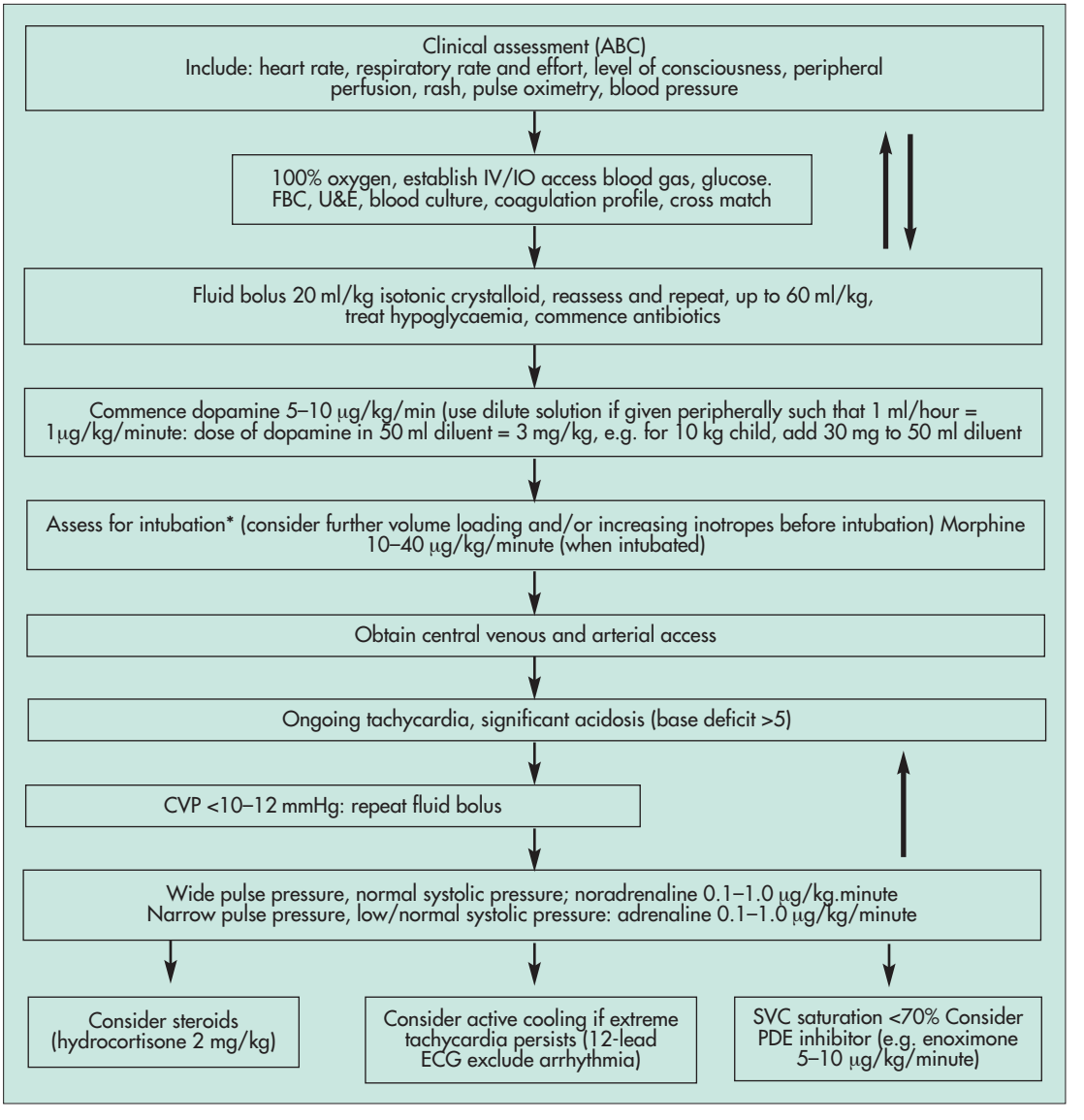
There is no ideal monitoring tool to quantify volume status. Patients requiring more than 40–50 ml/kg of fluid boluses with ongoing acidosis are likely to require further volume, as well as inotropic support, mandating placement of a central venous line.

It is reasonable, however, to assume that either a low absolute value or a downward trend in central venous pressure represent underfilling. Conversely, a normal or raised venous pressure can coexist with a relative hypovolaemic state in the presence of tricuspid regurgitation, poor right ventricular function, pulmonary hypertension or pericardial tamponade (Butt, 2001). Variations in arterial pulse pressure (Michard et al, 2000) and also in the pulse oximeter signal (Frey and Butt, 1998) have also been used to predict response to further fluid boluses.

Haemodynamic assessment

Approximately 70% of children with septic shock manifest a degree of cardiac dysfunction resulting in a low, or low-normal cardiac output; the highest mortality is seen when this occurs together with an elevated systemic vascular resistance (28% *vs* 10%) (Ceneviva et al, 1998). It is common for the haemodynamic profile to change, often dramatically during the septic episode, resulting in the initiation of seemingly diametrically-opposed therapies, e.g. substituting vasodilators for vasoconstrictors. It is therefore important to have a way of estimating the haemodynamic profile. Pulse pressure, measured via an intra-arterial catheter, may provide a useful indicator, provided that adequate volume resuscitation has occurred (Carcillo et al, 2002). A normal systolic pressure with a wide pulse pressure suggests preserved cardiac function and low vascular

Figure 2. Suggested initial resuscitation for septic shock (from Carcillo et al, 2002). *Intubation may occur earlier in the algorithm (as a part of the initial ABC) in the moribund child. ABC = airway, breathing, circulation; ECG = electrocardiogram; FBC = full blood count; IV = intraavenous; IO = intraosseous; PDE = phosphodiesterase; SVC = superior vena cava; U&E = urea, creatinine and electrolytes.



resistance ('warm shock'), while a narrow pulse pressure suggests reduced cardiac function ('cold shock'). Clinical signs, including, capillary refill time and core-peripheral temperature gradient, may aid differentiation between 'warm' and 'cold' shock; however, caution must be applied in the face of inadequate fluid resuscitation or fever (Tibby et al, 1999). Unfortunately, the terms 'warm' and 'cold' shock are rather arbitrary and represent extremes of a clinical spectrum.

Superior vena-caval oxygen saturation (measured via co-oximetry) provides a useful guide to the adequacy of the ratio of oxygen delivery to consumption. A low central-venous saturation represents a compensatory response to inadequate oxygen delivery and/or excessive oxygen consumption (via the Fick principle). Resuscitation algorithms incorporating this parameter have resulted in improved survival (Rivers et al, 2001). An elevated blood lactate may occur with inadequate oxygen delivery, either global or regional. The trend in this parameter is more important than considering a single measure in isolation (Duke et al, 1997, Hatherill et al, 2000). Care must be exercised when interpreting pH and base deficit as markers of 'metabolic wellbeing', as hyperchloraemia is common in shock, and may perpetuate a metabolic acidosis. This may be a result of the chloride-rich fluids (normal saline, human albumin solution) used during resuscitation (Skellett et al, 2000). Here, it is the serum chloride level relative to sodium that is important rather than the absolute chloride value; it has been suggested that a ratio of chloride to sodium >0.79 in the setting of a metabolic acidosis reliably diagnoses hyperchloraemia as the cause of the acidosis (Durward et al, 2001).

Inotropic and vasoactive medication

The typical mechanism for providing inotropic support to the failing myocardium is via beta-receptor stimulation. The common agents (dopamine and adrenaline) also provide a degree of alpha-receptor-related vasoconstriction at higher doses. Although primarily a vasoconstrictor, noradrenaline also possesses beta activity. Dobutamine exhibits little, or no, alpha activity (depending on whether it is given as a racemic preparation), and has been suggested as the initial resuscitation inotrope of choice as it may be administered peripherally. This agent, however, may produce an unacceptable degree of tachycardia secondary to vasodilatation, thereby reducing filling time and hence preload (particularly if diastolic dysfunction is present). In reality, it is not unreasonable to administer any of the inotropes in dilute solutions, either peripherally or via the intraosseus route, as a temporising measure until central venous access is established.

Unfortunately, high doses of beta agonists may be required in sepsis because of down regulation of the beta-receptors. This may result in diminished overall benefit because of excessive increases in oxygen consumption (predominantly via thermogenesis) relative to oxygen delivery, and provides a rationale for phosphodiesterase inhibitor usage (Barton et al, 1996). These agents (enoximone, milrinone) work by inhibiting the breakdown of cyclic AMP, and provide additional benefits of mild vasodilatation and augmentation of diastolic function.

An inverse relationship exists between contractility and afterload. This is often accentuated in sepsis-induced heart failure and provides the basis for administrating vasodilators; however, this is balanced by the need to maintain adequate organ perfusion pressures.

Other therapies

The need for mechanical ventilation must be considered for any child with ongoing metabolic acidosis requiring more than 40–50 ml/kg of volume resuscitation. It is a mistake to defer intubation for such a child on the basis that they are 'maintaining an airway' and 'have only a modest oxygen requirement'; this situation will usually deteriorate and represents a window of opportunity, thereby minimizing the risk from the anaesthetic induction agents. Intubation should be preceded by volume loading and commencement of inotropes (peripherally, if necessary). The benefits of positive pressure ventilation in this setting are multiple: amelioration of pulmonary oedema-induced hypoxia, augmentation of cardiac function through afterload reduction, decreasing oxygen consumption by minimizing the work of breathing and maximizing sedation, improving cerebral blood flow by avoiding spontaneous hypocarbia (a common event), and providing an opportunity to gain central venous access.

Hyperthermia is a common cause of excessive oxygen consumption. Accurate temperature measurement is often impossible in a severely shocked child; if the trunk feels hot to touch, then the patient is probably febrile. Another clue to 'occult fever' is severe tachycardia in the face of seemingly appropriate volume resuscitation. Simple antipyretics, such as paracetamol, may be insufficient, therfore other techniques such as application of crushed ice to the patient's head, or cold saline bladder and/or gastric lavage may be required.

The role of steroids is increasingly recognized, particularly in the setting of relative adrenal

insufficiency (Annane et al, 2002). It is not unreasonable to consider steroids for any patient who is exhibiting catecholamine-resistant shock (worsening acidosis and hypotension in the face of an increasing inotrope requirement). Consideration for other therapies, e.g. haemofiltration, activated protein C and strict glycaemic control, can usually be deferred until ICU admission (Vincent et al, 2002). **HM**

Conflict of interest: none

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KEY POINTS

- Sepsis and multiple organ failure contribute to over 90% of deaths in the paediatric intensive care unit (ICU).
- The incidence of severe sepsis has increased over the last 20 years, but the death rate has declined.
- The mortality from sepsis is highest in infants, and increases in the presence of significant co-morbidities.
- Multiple organ failure generally occurs within a few days of ICU admission.
- Consensus guidelines for the treatment of septic shock now exist.